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Pd(II)-Catalyzed *para*-Selective C−H Arylation of Monosubstituted Arenes

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Supporting Information

ABSTRACT: Pd-catalyzed highly *para*-selective C−H arylation of monosubstituted arenes (including toluene) is developed for the first time using an F^+ reagent as a bystanding oxidant. This finding provides a new retrosynthetic disconnection for *para*-substituted biaryl synthesis via C−H/C−H cross-coupling.

The electrophilic palladation of arenes observed in the 1960s mainly involves either highly reactive electron-rich arenes or excess benzene to promote palladation through high molarity.[1] Extensive efforts to exploit directed *ortho*-palladation to develop synthetically useful reactions have shown encouraging progress during the past decade.[2] Recently, mono-*N*-protected amino acid ligands have been demonstrated to enhance reactivity[3] and to control regio-[3a] and stereoselectivity.[4] From the viewpoint of synthetic applications, the next fundamental challenge in this field is to achieve *meta*- and *para*-selectivity with representative monosubstituted arene substrates.[5,6] Herein, we report the first example of highly *para*-selective arylation of monosubstituted arenes via a C−H/C−H coupling. This provides a unique route for accessing *para*-substituted biaryls, a structural motif found in antagonist drug molecules such as Losartan and Valsartan (Figure 1).[7] The combination of an acidic amide directing group for the first C−H activation step and a bystanding F^+ oxidant for the second C−H activation step is crucial for high *para*-selectivity.

Reactions that directly couple two aryl C−H bonds[8] have witnessed a recent resurgence in interest, owing to the prospect of achieving predominant cross-coupling by increasing the reactivity of one of the two arenes. This has been achieved by either using an electron-rich arene[9] or appending a directing group[10] onto one of the arenes to suppress undesired C−H/C−H homocoupling. Among numerous seminal contributions, recent reports by the Dong group using amide directing groups have shown the most encouraging substrate scope, including broadly useful benzoic acid and phenylacetic acid carbogenic skeletons, albeit only those containing electron-neutral and -rich arenes.[10g] A common problem in these reactions is the formation of an intractable mixture of regioisomers when a simple monosubstituted arene is used as the coupling partner, which compromises their synthetic utility. Although sterically less hindered C−H bonds were often preferentially activated with 1,2-disubstituted arene substrates, synthetically useful regioselectivity was achieved only with anisole by Buchwald[10d] ($o/m/p$ = 1/2/12) and Dong[10g] ($o/m/p$ = 1/1.4/8.6) when *mono*substituted arenes were used.

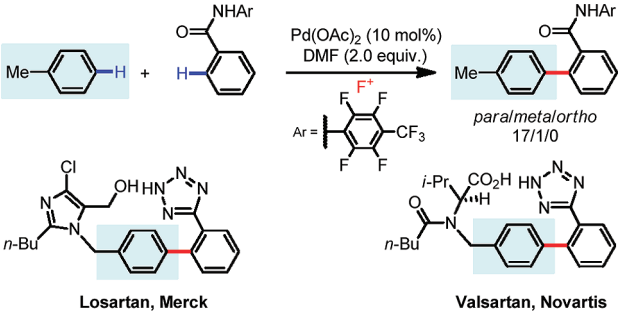
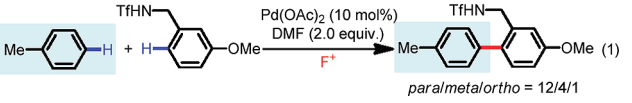


Figure 1. A new disconnection for *para*-substituted biaryl synthesis.

We recently employed F^+ reagents as bystanding oxidants to promote selective C−N and C−O reductive elimination from Pd(IV) in a number of C−H functionalization reactions.[11] Michael and co-workers observed that a [Pd(II)-alkyl] intermediate generated from the carboamination of olefins reacted with toluene in the presence of *N*-fluorobenzenesulfonimide (NFSI) to give mainly *para*-alkylated toluene compounds as the isolated products in 45−90% yields.[12] In our previous fluorination of benzyltriflamide with F^+,[13a] a small amount of *ortho*-arylation product (<10%) was also formed when toluene was used as the solvent. In this case, toluene was activated with moderate selectivity ($o/m/p$ = 1/4/12) (eq 1).



Guided by these observations, we began to search for a suitable combination of directing group and reaction conditions that would allow highly *para*-selective arylation of toluene. Since the acidic amide as a carboxylic acid mimic derived from 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline ($ArNH_2$) has demonstrated superior reactivity for C−H activation,[14] we focused on amide **1a** and screened oxidants and additives known to promote C−H activation (Table 1). We found that the use of the F^+ reagent 1-fluoro-2,4,6-trimethylpyridinium triflate (NFTMPT) and 2 equiv of DMF as an additive promoted the arylation of toluene to give the desired product in 70% yield with a *para*/*meta* ratio of 13/1 (entry 14). No *ortho*-arylation was observed. Intriguingly, replacing NFTMPT with the previously reported oxidant $K_2S_2O_8$[10g] gave the arylated products with poor selectivity (*para*/*meta*, 1.7/1; entry 13). Considering the result shown in

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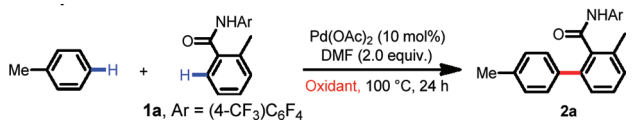
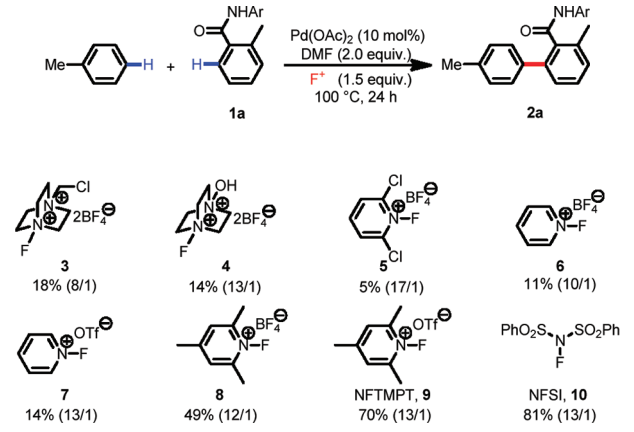
Table 1. Pd(II)-Catalyzed Oxidative C−H/C−H Cross-Coupling: Survey of Oxidants[a],



entry	oxidant (equiv)	yield[b] (%)	entry	oxidant (equiv)	yield[b] (%)
1	AgOAc (3.0)	0	8	$(PhCOO)_2$	0
2	$Cu(OAc)_2$ (1.5)	0	9	NCS (1.5)	0[d]
3	$AgOAc/CuCl_2$ (1.5/1.5)	0	10	$PhI(OAc)_2$ (1.5)	0[e]
4	$PhCO_3t$-Bu (1.5)	0	11	$PhI(TFA)_2$ (1.5)	0
5	oxone (3.0)	0	12	$PhI(OPiv)_2$ (1.5)	0
6	$Ce(SO_4)_2$ (2.0)	0	13[c]	$K_2S_2O_8$ (3.0)	75 (1.7/1)[f]
7	$(t\text{-BuO})_2$ (1.5)	0	14	NFTMPT (1.5)	70 (13/1)[f]

[a] Unless otherwise noted, the reaction conditions were as follows: amide **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1.5 equiv), DMF (2.0 equiv), toluene (2 mL), 100 °C, 24 h. [b] Isolated yield. [c] CF_3COOH (5 equiv) was added. [d] Chlorinated product was formed in 40% GC yield. [e] Acetoxylated product was formed in 45% GC yield. [f] Regioselectivity determined by GC analysis (*para*/*meta*) is shown in parentheses.

Table 2. Survey of F^+ Oxidants[a,b,c]



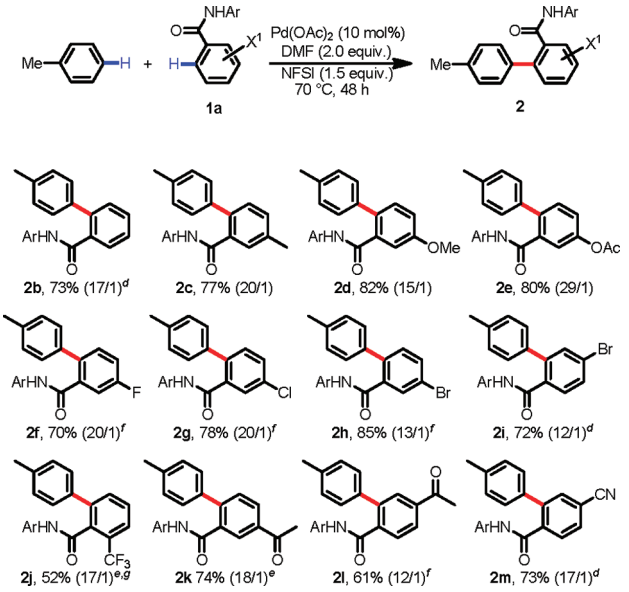
[a] Unless otherwise noted, the reaction conditions were as follows: amide **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1.5 equiv), DMF (2.0 equiv), toluene (2 mL), 100 °C, 24 h. [b] Isolated yields are given. [c] Regioselectivity determined by GC analysis (*para*/*meta*) is shown in parentheses.

eq 1, these experimental observations suggest that both the directing group and the F^+ reagent are crucial for obtaining high *para*-selectivity.

With the insight that F^+ reagents are crucial for *para*-selectivity, we next tested various F^+ sources. In all cases, uniformly high *para*-selectivity was observed, and NFSI gave the highest yield (Table 2).

Under these optimized conditions, an array of synthetically useful benzamides was reacted with toluene (Table 3). Benzamides containing no substituent and those substituted with electron-donating groups were arylated smoothly to give the

Table 3. Scope of Benzamides[a,b,c]



[a] Unless otherwise noted, the reaction conditions were as follows: amide **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1.5 equiv), DMF (2.0 equiv), toluene (2 mL), 70 °C, 48 h. [b] Isolated yields are given. [c] Regioselectivity determined by GC analysis (*para*/*meta*, no *ortho*-product was observed) is shown in parentheses. [d] 90 °C, 24 h. [e] 80 °C, 36 h. [f] 100 °C, 24 h. [g] 15 mol % $Pd(OAc)_2$.

corresponding biaryl products with excellent *para*-selectivity with respect to toluene (**2b**−**e**). A number of halogenated benzamides also reacted with toluene with similarly high regioselectivity to give the biaryl products in good yields (**2f**−**i**). The chloro and bromo substituents are useful handles for further synthetic elaboration. Of special importance, benzamides containing electron-withdrawing groups including trifluoromethyl, ketone, and cyano groups are also compatible with this catalytic system (**2j**−**m**). Notably, previously reported C−H/C−H coupling reactions were typically low-yielding with electron-deficient substrates, except for highly reactive pentafluorobenzene,[10] which illustrates the efficiency of this acidic amide directing group in C−H/C−H coupling reactions.

High levels of *para*-selectivity were consistently observed with other substituted arenes containing alkyl, methoxy, and halo groups (Table 4). The compatibility of halides with the reaction conditions allows for additional synthetic elaboration through venerable Pd(0)-catalyzed cross-coupling and Buchwald−Hartwig amination reactions. The amide products could be readily converted to carboxylic acids as useful intermediates for the synthesis of drug molecules such as Losartan and Valsartan (treating with TFA/H_2O (4/1) at 90 °C; see Supporting Information).

The exceedingly high *para*-selectivity observed for such C−H/C−H coupling reactions could have significant mechanistic implications. Since the first C−H activation step involving this acidic amide directing group is relatively well understood,[14] we focused on the second C−H activation step. By comparing the initial reaction rate of toluene to that of toluene-d_8, k_H/k_D was determined to be 1.0 (Figure 2), which is consistent with an electrophilic palladation mechanism if we consider the first C−H activation step to be a relatively fast step.

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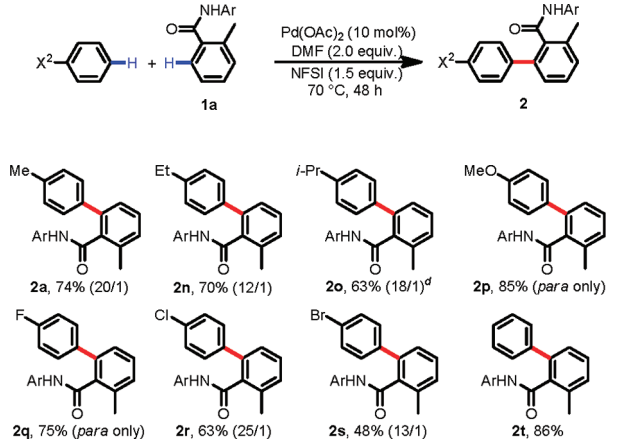
Table 4. Scope of Monosubstituted Arenes[a,b,c]



[a] Unless otherwise noted, the reaction conditions were as follows: amide **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), NFSI (1.5 equiv), DMF (2.0 equiv), arene (2 mL), 70 °C, 48 h. [b] Isolated yields are given. [c] Regioselectivity determined by GC analysis (*para*/*meta*, no *ortho*-product was observed) is shown in parentheses. [d] 100 °C, 24 h.

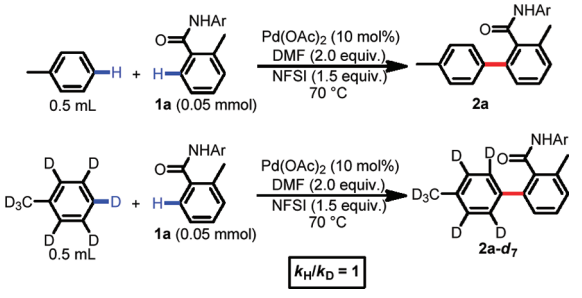


Figure 2. Kinetic isotope effect.

The low selectivity observed with other oxidants such as $Na_2S_2O_8$[10g] seems to suggest that the [ArPd(IV)F] species is partially responsible for selective *para*-C−H cleavage. (This statement holds true only if [ArPd(IV)F] species are formed under these conditions.) We also isolated around 5% *ortho*-fluorinated product using amide substrate **1a**, which serves as evidence for the formation of an [ArPd(IV)F] intermediate. We have recently further shown that the fluorination could occur as a major pathway under suitable conditions in the absence of arene coupling partners.[13b] Although direct evidence for the involvement of Pd(IV) complexes in the cleavage of the *para*-C−H bond is lacking, oxidation of Pd(II) to Pd(IV) species by F^+ was previously established as a facile process.[15] In addition, C−H cleavage by isolated Pt(IV)[16a] or proposed Pd(IV) complexes[12,16b] was reported. The significantly lower *para*-selectivity observed with the triflamide directing group (eq 1) indicates that the directing group also has a great impact on the regioselectivity.

In summary, we have developed a C−H/C−H coupling of benzamides with monosubstituted arenes including toluene. When our amide directing group was used in conjunction with a bystanding F^+ oxidant, high *para*-selectivity was achieved. Electron-withdrawing groups such as ketone and cyano are tolerated on one of the coupling partners. Further development of this type of reaction to allow the use of 1 equiv of arenes could potentially lead to practical new tools for the synthesis of *para*-substituted biaryls.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization of all new compounds; complete ref 7b. This material is available free of charge via the Internet at http://pubs.acs.org.

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